Can ErbB2 overexpression protect against doxorubicin cardiotoxicity?

Petra Rocic
Department of Pharmacology, New York Medical College, Valhalla, New York

Identification of the human epidermal growth factor receptor (HER2/ErbB2) as a target for therapy in HER2/ErbB2-positive breast cancer was a huge milestone in treatment of these typically highly aggressive cancers. At 8-yr follow-up, trastuzumab, a monoclonal antibody against HER2/ErbB2, increased survival by ~40% compared with standard chemotherapy: anthracycline (doxorubicin), cyclophosphamide, and paclitaxel (11). Unfortunately, trastuzumab turned out to be severely cardiotoxic, leading to serious complications including left ventricular dysfunction and heart failure, with approximately three times greater incidence than anthracyclines (doxorubicin) alone (27 vs. 8% of patients at 1 yr of therapy) (14, 15). This is even further concerning when considering that anthracyclines themselves have considerable documented cardiotoxicity: ~8% at 1 yr, 6-18% at 2 yr (4, 13), and ~40% at 20 yr (5) postcompletion of treatment. As might be expected, because of the efficacy of anti-HER2/ErbB2 antibodies in the treatment of cancer, discovery of their cardiotoxicity prompted considerable research effort into mechanisms by which ErbB2 regulates cardiac function.

For over a decade, it has been known that a major increase in oxidative stress was the primary mechanism of doxorubicin-mediated cardiotoxicity (13). Oxidative stress has also been implicated as a mechanism for trastuzumab-induced cardiac dysfunction (6). ErbB2 antagonism in cardiac myocytes increased oxidative stress and cell death by increasing reactive oxygen species (ROS) and inducing mitochondrial apoptotic signaling (5). In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, the study by Belmonte et. al. (1) extends these findings to demonstrate that cardiac-specific ErbB2 overexpression is able to upregulate mitochondrial antioxidant defenses (glutathione peroxidase-1 expression, glutathione peroxidase activity, and catalase expression) and downregulate hydrogen peroxide in the mitochondria.

Mitochondrial oxidative stress plays a critical role in cardiovascular disease progression, including in the transition from compensatory hypertrophy to overt heart failure. Mitochondrial DNA (mtDNA) is more susceptible to damage by ROS due to lack of histones and thus greater accessibility to ROS and limited DNA repair enzyme capabilities in the mitochondria. Increased mtDNA damage translates into aberrant synthesis of proteins of the mitochondrial respiratory chain and eventual respiratory chain dysfunction (16). This then results in further ROS production, resulting in a cycle of amplification of ROS and mtDNA damage, which eventually leads to a critical drop in cellular ATP levels, Ca2⁺ overload, and myocyte death. Thus discovering that ErbB2 specifically modulates mitochondrial ROS levels in the heart may be important since this may elucidate the mechanism by which ErbB2 regulates mitochondrial and cardiac dysfunction.

In addition, the authors show that Abelson murine leukemia cellular oncogene homolog 1 (c-Abl) and Abelson-related gene (Arg) were upregulated by ErbB2 overexpression (1). c-Abl can transactivate the epidermal growth factor receptor through the Ras-Raf-extracellular signal recognition kinase 1/2 mitogen-activated protein kinase pathway as well as directly activate the phosphatidylinositol 3-kinase-Akt pathway (9), a major prosurvival signaling pathway in several cell types including cardiac myocytes. This is in agreement with the reported downregulation of Akt activation by ErbB2 antibodies in cancer cells and cardiac myocytes (5). Therefore, identification of these ErbB2-dependent signaling pathways in the heart in vivo are of potential translational significance with the goal of preserving cardiac function through decreasing myocyte cell death.

There are limitations in extending the novel mechanistic aspects of the present study to the function and therapeutic targeting of this system in vivo, which will need to be investigated in future studies. First, the effects of ErbB2 overexpression on cardiotoxicity are not examined in adult cardiac myocytes or in the whole heart in vivo. Cardiotoxicity is instead evaluated in neonatal myocytes in cell culture. Neonatal and adult myocytes differ in many significant parameters relevant to cell survival, including sensitivity to altered Ca2⁺ and ATP concentrations and oxygen consumption. Therefore, results from neonatal myocytes cannot be automatically translated to adult myocytes.

Second, while this study shows that ErbB2 overexpression in the heart increases certain aspects of the cellular antioxidant defense machinery and reduces ROS, it remains to be demonstrated if it is able to achieve this effect in the face of a doxorubicin or anti-HER2/ErbB2 antibody challenge, i.e., if the ErbB2 overexpressing animals were treated with a chemotherapeutically effective dose of doxorubicin and/or trastuzumab, would ErbB2 overexpression still be able to prevent the increase in ROS?

Third, this study demonstrates that ErbB2 overexpression maintains normal oxygen consumption and mitochondrial complex I activity. However, neither ATP production nor Ca2⁺ concentrations was measured. Increased mitochondrial ROS production is frequently coupled to decreased ATP production. Mitochondrial ATP production has been shown to be decreased specifically in doxorubicin-induced heart failure (2). Decreased ATP production leads to Ca2⁺ overload, mainly due to consequent failure of the sarcolemmal reticulum Ca2⁺ ATPase 2 and the Na⁺/K⁺ ATPase leading to decreased activity of the Na⁺/Ca2⁺ exchanger, and heart failure. Therefore, it would be important to examine these parameters and cardiac function in future studies.

In summary, based on the findings presented in this study, it is difficult to form definitive conclusions regarding the protective effect of HER2/ErbB2 overexpression in the heart against doxorubicin- or trastuzumab-induced cardiotoxicity, either
short or long term. Combined doxorubicine and trastuzumab regimen, constructed to mimic cycles of chemotherapy for HER2/ErbB2-positive breast cancer in humans, had a syner-
gistic detrimental effect on both left and right ventricular function in mice, inducing biventricular failure in only 2 wk (7). Moreover, ventricular-restricted deletion of ErbB2 in mice resulted in multiple independent parameters of dilated cardio-
myopathy, including chamber dilation, wall thinning, and de-
creased contractility (3). Thus evaluation of heart failure in
ErbB2 overexpressing animals, or in the presence of an inter-
vention that increases ErBb2 expression, in response to treat-
ment with chemotherapeutically effective dose of doxorubicin
and/or trastuzumab in future studies could help determine
whether this system can protect against cardiac dysfunction
caused by these agents.

A limitation of the majority of human and animal therapeutic
studies related to doxorubicin and/or trastuzumab is that they
do not consider an extended follow-up period. Similar to the
study by Belmonte et al., a new pilot clinical trial with
trastuzumab emtansine (TDM1), the HER2/ErbB2 antibody
conjugated to a tubulin-binding agent that disrupts microtubule
assembly, reported a 10% asymptomatic decline in left ven-
tricular function in 3% of patients at a short 2-year follow-up and
did not consider this significant (6). However, it is becoming
increasingly apparent that doxorubicin-induced cardiotoxicity
manifests as continual increase in incidence of sustained echo-
cardiographic abnormalities, including overt heart failure, and
affects ~40% of patients 20 yr after conclusion of therapy (12)
versus ~8% at 1 yr posttherapy (14). Thus it might be advis-
able that future basic science animal studies and clinical studies
that aim to evaluate cardiotoxicity of anthracycline- and HER2/
ErbB2-based therapies extend follow-up time.

Overall, the study from Belmonte and colleagues (1), which
examines the effects of cardiac-specific ErbB2 overexpression,
provides novel evidence that it provides cardiac protection
through upregulation of mitochondrial antioxidant defenses,
glutathione peroxidase 1 and catalase, and lowering of mito-
chondrial hydrogen peroxide. While this is likely to be an
important target to prevent the pathological transition into
overt heart failure, further studies are needed to establish its
mechanism of action and potential therapeutic benefits. One
potential mechanism is through preserving microvascular den-
sity. Coronary microvascular rarefaction has been associated
with pathological (vs. exercise induced) cardiac hypertrophy
and predicts transition to heart failure (dilated cardiomyopathy)
(8). It has recently been demonstrated that decreasing specifi-
cally mitochondrial oxidative stress is necessary for restoration
of coronary arteriogenesis (11). Similar, mitochondrial oxida-
tive, stress-dependent mechanisms could also apply to angio-
genesis. ErbB2 overexpression, because it apparently regulates
mitochondrial oxidative stress, could feasibly facilitate both
processes.

GRANTS

This work is supported by National Heart, Lung, and Blood Institute Grant
R01-HL093052.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

P.R. drafted, edited and revised, and approved final version of manuscript.

REFERENCES

1. Belmonte F, Dac S, Syssa-Shah P, Sivakumaran V, Stanley B, Guo X,
Paolucci N, Ann MA, Nagane M, Kuppusamy P, Steenbergen C,
Gabrielson K, ErbB2 overexpression upregulates antioxidant enzymes,
reduces basal levels of reactive oxygen species, and protects against
doi:10.1152/ajpheart.00517.2014.

3rd. Uncoupling protein downregulation in doxorubicin-induced heart
failure improves mitochondrial coupling but increases reactive oxygen

ErbB2 is essential in the prevention of dilated cardiomyopathy. Nat Med 8:

4. Ewer MS, O’Shaughnessy J. Cardiac toxicity of trastuzumab-related
remissions in HER2-overexpressing breast cancer. Clin Breast Cancer 7:

5. Gordon LR, Burke MA, Singh AT, Prachand S, Lieberman ED, Sun L,
Nak T, Prasad SV, Ardehali H. Blockade of the erbB2 receptor induces

ML, Campone M, Xu N, Smith M, Gianni L. Feasibility and cardiac
safety of trastuzumab emtansine after anthracycline-based chemotherapy

7. Milano G, Raucci A, Scoope A, Daniele R, Guerrini U, Sironi L,
Cardinale D, Capogrossi MC, Pompilio G. Doxorubicin and trastu-
zumab regimen induces biventricular failure in mice. J Am Soc Echocar-

8. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Malezewski
JJ, Redfield MM. Coronary microvascular rarefaction and myocardial
fibrosis in heart failure with preserved ejection fraction. Circulation 131:

9. Pan C, Olsen JY, Daub H, Mann M. Global effects of kinase inhibitors
on signaling networks revealed by quantitative phosphoproteomics. Mol

10. Perez EA, Ramond EH, Suman VJ, Jeong JH, Sledge GW, Davidson NE, Mamounas E, Zujewski JA, Wolmark N. Trastu-
zumab plus adjuvant chemotherapy for human epidermal growth factor

V, Guarini G, Yin L, Chilian WM. Resolution of mitochondrial oxida-

Hodgson DC. Echocardiographic detection of cardiac dysfunction in
childhood cancer survivors: How long is screening required? Blood Cancer
J 5: e2561. [Epub ahead of print].

V, Vergely C. Anthracyclines/trastuzumab: new aspects of cardiotoxicity and

L. Use of chemotherapy plus a monoclonal antibody against HER2 for
metastatic breast cancer that overexpresses HER2. N Engl J Med 344:
783–792, 2011.

15. Spano JP, Azria D, Goncalves A. Patients’ satisfaction in early breast
cancer treatment: change in treatment over time and impact of HER2-

16. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart